LITERATURE EVALUATION

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Learning Objectives

1. Justify the need for literature evaluation to optimize drug therapy.
2. Compare and evaluate the different types of resources available to assess and resolve drug-related problems.
3. Assess the different sections of a published study for comprehensiveness and quality.
4. Distinguish between the different types of clinical trial designs and determine the appropriateness of each for the research hypothesis in question.
5. Evaluate the primary literature for the presence of bias and confounding variables to determine their effect on validity and applicability.
6. Apply the concepts and techniques reviewed in this chapter to critically evaluate the medical literature and applicability of these results to patient care.

Introduction

Literature evaluation is a skill that most pharmacists think they possess but also think they could improve. Literature evaluation skills are developed with repeated use, as it is only with practice that pharmacists can learn to identify limitations and determine the internal and external validity of a clinical trial. Pharmacy students typically believe that "if it is published, then it must be true" because all articles are reviewed before they are published. However, pharmacy students quickly learn, after their preceptor points out countless limitations in the seemingly perfect article they are presenting during journal club, that most, if not all, articles have limitations. With the biomedical literature expanding at an incredible rate, literature evaluation skills are critical to determine which articles should change pharmacists' current practice. Pharmacists frequently are faced with questions during rounds regarding recently published articles and need to have the skills to decide if the results of these trials should be applied to patient care. Pharmacists involved with the pharmacy and therapeutics committee of a hospital also have to evaluate critically the literature to determine if a drug should be included on the formulary. In addition, the increased complexity of clinical trials has made literature evaluation more difficult. Therefore, pharmacists need to improve their literature evaluation skills to decide which information to incorporate into their clinical practice.

Systematic Approach

When presented with a question related to drug therapy, pharmacists routinely follow certain steps. The systematic approach was first developed in 1975 as a strategy to teach pharmacy students drug information skills and was originally a five-step process. The modified systematic approach is a series of seven steps that promotes effective and efficient responses to drug information requests. This approach has improved the quality of responses to drug information requests. Table 1-1 lists the seven steps of the modified systematic approach. The first three steps of this process help to ensure that the pharmacist truly understands the question. Frequently, pharmacists are asked a question from a patient or health care professional only to find out later that what the person actually wanted to know differed from the original question posed. Obtaining background information helps the pharmacist to understand all aspects of the clinical situation and the intent of the question being asked. This procedure saves valuable time and allows the pharmacist to search efficiently for the answer to the question. The fourth step, developing a search strategy and conducting a search, can be complicated, depending on the resources the pharmacist has available. However, understanding the advantages and disadvantages of

available resources helps the pharmacist efficiently determine the best search process.

The fifth step in this process involves evaluation, analysis, and synthesis of information. This step allows the respondent to put to use the literature evaluation skills he or she has developed. Without this step, the response often will be simply a regurgitation of the information found. It is important for a well-trained pharmacist to consider thoroughly all aspects of the clinical problem and to use evidence to develop the response (sixth step). The final step, conduct follow-up and documentation, is necessary to determine if the recommendation was accepted and implemented.

In general, it is best to follow an organized, stepwise approach when searching the drug information literature. This process involves a search that starts with the tertiary literature, followed by the secondary literature and primary resources. The tertiary literature provides quick access to information and serves to provide the reader with background knowledge of the topic. Secondary resources typically are used when the information in the tertiary references is out-of-date or incomplete, which often is the case with new drugs or new uses for older drugs. The primary literature is consulted when more current or in-depth information is needed; however, a limitation to using the primary literature is that it can be biased and requires critical evaluation. Searches that rely solely on the primary literature can be incomplete, depending on the search techniques used and the databases available. Information is less likely to be missed if the tertiary literature is consulted first. For example, although rare adverse events often will not be mentioned in clinical trials or review articles, they most likely will be listed in MICROMEDEX. In some situations, a search of the tertiary literature may be omitted if the pharmacist is certain that the information would not be found; however, if the pharmacist is unfamiliar with the disease or drug being investigated, reading the tertiary literature can help to improve the pharmacist's search of the secondary and primary literature. For example, identifying search terms to use in MEDLINE can be difficult if all aspects of the disease are not fully understood.

Tertiary References

Tertiary references include general textbooks (e.g., Pharmacotherapy: A Pathophysiologic Approach), compendia (American Hospital Formulary Service, Drug Facts and Comparisons, and Physicians' Desk Reference), and computer databases (MICROMEDEX). Review articles and information found on the Internet also are considered tertiary references. Review articles can be divided into systematic reviews and nonsystematic or narrative reviews. Systematic reviews clearly specify the methods used to identify and summarize the information collected. Meta-analysis is a type of systematic review that is discussed in detail in the Primary References section. Narrative reviews summarize previously conducted research but do not specify the methods used to identify and summarize the information. For articles reviewing drug therapy, systematic reviews typically are preferred over narrative reviews. Narrative reviews can be subject to bias because of conflicts of interest. The purpose of tertiary references is to summarize the current standard of practice. Tertiary references are used by pharmacists frequently because they are easy to use, convenient, concise, and compact. However, it is important to consider their potential disadvantages. Textbooks often are out-of-date because the information is sometimes written 1–2 years before it is published, and most tertiary references are only updated every 2–5 years; however, many tertiary references, such as some drug interaction resources, are updated quarterly. Also, because the information must be presented in a compact format, many topics may not be reviewed in detail because of space limitations. Some authors may leave out information that they do not feel is important to allow for more detail on other topics. These limitations of the tertiary references require an appropriate search for primary literature when more up-to-date information or more detailed information is needed. Important characteristics to consider when evaluating the tertiary literature are listed in Table 1-2.

Table 1-1. The Modified Systematic Approach to Answering Questions on Drug Therapy

Step 1.	Secure demographics of the requestor
Step 2.	Obtain background information that leads to the question
Step 3.	Determine and categorize the ultimate question
Step 4.	Develop a strategy and conduct a search
Step 5.	Perform evaluation, analysis, and synthesis
Step 6.	Formulate and provide a response
Step 7.	Conduct follow-up and documentation

Table 1-2. Evaluation of the Tertiary Literature

Expertise of the author
Purpose of the book
Edition and year of publication
References cited
Ease of use
Format—textbook, computerized
Availability of network versions

Secondary References

Secondary references are resources that are used to identify primary references when the information contained in the tertiary literature appears out-of-date or incomplete. Many questions can be answered using tertiary resources; however, questions on new uses of a drug or recent reports of drug interactions or adverse effects require searching the primary literature. Secondary references consist of indexing and abstracting services. Indexing services only provide the article citation and possibly the authors' abstract of the article. Abstracting services provide the citation as well as an abstract written by someone other than the original author. Secondary references frequently are published as newsletters, although most of the larger databases are available electronically. There are a variety of secondary references, each with different benefits.

Although MEDLINE is easily accessible, that there are other secondary references that can be useful in certain situations. For example, International Pharmaceutical Abstracts is a secondary reference that covers many pharmacy journals that are not included in MEDLINE; therefore, questions pertaining to issues specific to pharmacy may not be found in MEDLINE but would be found in International Pharmaceutical Abstracts. Examples include questions on compounding or on stability and compatibility of drugs. Important aspects to consider when evaluating the quality of a secondary reference include: number of journals reviewed, frequency of publication or updates, types of journals included, cost, and abstracting versus indexing services. Secondary references that cover a greater number of journals and are updated more frequently typically are preferred; however, these two factors affect the cost of the reference as well. Table 1-3 lists the most common secondary references that are available.

How to Search Secondary References

Understanding how to search databases is critical to their effective use. Many databases allow free-text searching which means the database will search for the terms users enter anywhere in the title or text of the document; this type of search can lead to irrelevant results because the main topic of the article could be unrelated to the terms entered. However, most of the databases have a controlled vocabulary that allows for a more effective and efficient search. This controlled vocabulary is used to index the articles that are included in the database. Most articles are given 10–15 terms that describe the major topics of the article. These terms usually include the keywords that an author will submit with his or her manuscript. When searching the database for a particular article, using the controlled vocabulary will result in a more efficient search. The controlled vocabulary in MEDLINE is called Medical Subject Headings. MEDLINE contains a Medical Subject Headings browser (link located on the toolbar) that can be searched to find the appropriate search terms. Once a Medical Subject Headings term is selected, subheadings also can be selected that narrow the search further. Examples of subheadings available for drugs include administration and dosage, therapeutic use, adverse effects, and pharmacokinetics. The Medical Subject Headings browser also will provide users with the "trees" that are the hierarchal structure for the Medical Subject Headings terms, which allow users to broaden or narrow their search.

Most computerized databases use Boolean operators to combine search terms. The three most frequently used Boolean operators are "AND", "OR", and "NOT". Other limiting factors that can be used include age, language, publication type, publication date, and whether the study was a human or animal trial. These additional limits are available, depending on the database. It typically is recommended to start a search with only one or two limits to avoid eliminating too many articles; more limits can be applied after the original search results are reviewed.

Table 1-3. Available Secondary References

MEDLINE	Includes more than 4600 journals with more than 12 million records; about 25% are foreign; author abstracts provided.
PubMed	PubMed provides access to MEDLINE as well as some additional citations that precede MEDLINE or are beyond the scope of those citations included in MEDLINE.
International Pharmaceutical Abstracts	An abstracting database with information pertinent to pharmacy and pharmaceutical sciences; covers about 800 journals; considered the secondary reference to use for pharmacy-related questions. Print and online versions available for about $400 and $3,000, respectively.
EMBASE	Similar to MEDLINE; however, it covers more foreign journals; includes more than 4000 journals with more than 9 million records; print, CD-ROM, and online versions.
ClinAlert	An abstracting service for adverse drug reaction reports; published twice per month in newsletter format; reviews about 100 journals; about $100/year.
Reactions Weekly	An abstracting service; published weekly in newsletter format; more extensive than ClinAlert; summarizes information on adverse drugs reactions, drug interactions, and toxicology; $1,260/year.
Iowa Drug Information System	An electronic indexing service that includes full text articles for about 200 English-language journals available on microfiche ($3,400/year), CD-ROM ($3,800–$5,300/year), and online (variable rate).
Journal Watch	An abstracting service provided by the publishers of the New England Journal of Medicine; summarizes articles published in the general medicine literature; covers 50 journals; $108/year.
Current Contents	Provides table of contents for more than 7500 different journals; author abstracts provided; available in print ($442/year), CD-ROM ($600–$1,000/year), and online (variable).

Primary References

The primary references consist of only studies or original reports of data published in biomedical journals; therefore, not all articles published in journals are considered to be primary references. The primary literature is used to obtain

the most recent information available on a topic. Tertiary references should always be consulted for background information and to understand the standard of care for a disease. The primary literature provides the reader with the details of how the study was conducted and how conclusions were drawn. This allows the reader to analyze and evaluate the methods of the study to determine if they are standard of care for the diagnosis and treatment of the disease and applicable to the patients in the reader's clinical practice. Many published papers contain methodological flaws; therefore, thorough literature evaluation is critical. Literature evaluation is a skill that health care professionals develop with practice; it requires knowledge in several areas, including clinical trial design, outcome measures, and statistical techniques. Most primary articles follow a standard format, which includes a title, authors, abstract, introduction, methods, results, and discussion.

Bias, Validity, and Confounding Variables

Before describing the various types of clinical trial designs, the terms bias, validity, and confounding variables need to be defined. Bias is a systematic error that affects the result either positively or negatively; it is something that affects the study results other than the treatment under investigation. There are many different types of bias. Table 1-4 summarizes the types of bias commonly seen in medical literature. Bias can be introduced in many ways, and investigators should take steps to minimize bias in their trial through randomization, control groups, blinding, the use of objective outcome measures, and the ability to account for all enrolled patients at the end of the study.

Table 1-4. Types of Bias

Prevalence—occurs when time elapses between exposure or diagnosis and enrollment in a trial
Admission rate—occurs when the hospital admission rate differs between the groups studied
Nonresponse—occurs when patients fail to respond to a survey or questionnaire
Membership—occurs when patients have more than one characteristic in common that is related to the disease under investigation
Procedure selection—occurs when patients are assigned to treatment based on certain characteristics rather than through randomization
Procedure—occurs when all treatment groups do not receive the same diagnostic procedures which leads to increased detection of the disease in one group
Recall—occurs when patients are asked to recall events in the past
Insensitive measure—occurs when the instruments used are not sensitive enough to detect the disease
Detection—occurs when a new technique for diagnosis is developed that detects the disease sooner, resulting in improved care or increased survival
Compliance—occurs when patients are more complaint with one treatment compared to the other treatment
Selection—occurs when inclusion or exclusion criteria limit the population to a degree that affects the extrapolation of the data
Observer—occurs when the patients are observed by different physicians or nurses
Interviewer—occurs when interviews are not conducted in the same manner for all patients or at all centers

Validity of a trial can be categorized as being internal or external. Internal validity refers to how the trial was conducted and determines if the results of the trial reflect what was intended to occur. For example, if the investigators of a randomized, controlled, double-blind trial were not adequately blinded to which patients received drug A versus drug B, then the internal validity of this trial could be adversely affected. Excessive dropouts also can adversely affect the internal validity of a clinical trial. Investigators should account for all enrolled patients at the end of the study because dropouts can affect results, especially if the disease is more severe. The use of an intent-to-treat analysis is the best way to handle dropouts. External validity refers to how well the results of the study can be applied to the patient population being cared for by the reader. If the study patients or conditions are not similar to those that commonly are seen in clinical practice, then the external validity of the trial is low because it cannot be applied to patient care. For example, if a trial of patients with type 2 diabetes excluded patients with concomitant hypertension and the patient population in the researching pharmacist's clinic primarily consists of patients with type 2 diabetes and hypertension, then the external validity of this trial could be low.

Confounding variables primarily are related to the condition being studied and, therefore, may affect the outcome. For example, confounding variables in a study that could affect the development of asthma would be allergies, smoking, and atopic diseases. Patients having these characteristics would affect the outcome of the study, particularly if the number of patients with these characteristics was unequal in each treatment group. Investigators can control for confounding variables through exclusion criteria, restricted randomization, stratification, and matching. Confounding variables also can be adjusted for in the statistical analyses.

Clinical Trial Design

Clinical trials are conducted to prove or disprove a hypothesis. The strength, or ability to prove causality, of the types of clinical trial conducted varies based on the type of design chosen. Randomized, controlled, clinical trials are considered the strongest design for determining cause and effect. Results from cohort and case-control studies are weaker, followed by cross-sectional studies and case reports or case series. Systematic reviews or meta-analyses are considered by some to be stronger than a randomized, controlled trial, but others believe that these reviews are just below randomized, controlled trials in strength. There are examples in the literature where the results of an adequately powered clinical trial do not match the results of prior meta-analyses. Other types of quasiexperimental observational designs, such as the before and after design commonly seen

in the pharmacy literature, are discussed in the Secondary Data Analysis/Observational Research chapter.

Although randomized, controlled trials are the gold standard for determining cause and effect, there are many types of clinical trial design that need to be understood and evaluated. Studies can be categorized as observational or interventional. Observational studies are those in which the investigator observes the events without any intervention, and in an interventional study, the participants receive an intervention (e.g., study drug). Experimental studies involve an intervention and are controlled. Experimental studies can be parallel or crossover in design. Parallel studies involve patients being assigned to one of the two or more treatments for a period of time, whereas patients in a crossover study will receive all drugs being evaluated in the study by being "crossed over" to the other treatments at defined intervals. Figure 1-1 graphically depicts parallel and crossover designs. Parallel studies are preferred for acute diseases or for diseases in which the treatment is curative. Crossover studies are best for chronic diseases, such as osteoarthritis, or for pharmacokinetic studies; however, they are not suitable for acute conditions, such as postoperative pain or infections.

In a crossover study, each person serves as his or her own control; therefore, variation between treatment groups is minimized. Because of the decreased variability, crossover studies are more powerful and require the inclusion of fewer patients than parallel studies. Although it should be noted that crossover studies have limitations as well. All crossover studies require the use of a washout period to allow for the effects of the first treatment to dissipate before treatment with the second drug is begun (to eliminate carry-over effect). A typical washout period should be at least five half-lives of the study drug or its active metabolite to allow for its complete elimination from the body. Another challenge with crossover studies often is the chronic nature of the disease being treated. For many chronic diseases, patients improve and relapse at any time; therefore, symptoms can be more severe during treatment with drug A than with drug B simply because of the time course of the disease and not because of the treatment (period effect). For example, this would be involved in studies of patients with allergic rhinitis and asthma because improvements or exacerbations in the disease can occur during certain seasons of the year. Dropouts in crossover studies can have a significant impact on results because two sets of data (i.e., patient data in each treatment arm) can be lost and, therefore, should be minimized. In addition to these problems with crossover designs, it is important that crossover studies are properly blinded and that patients are randomized to prevent bias.

Studies are conducted retrospectively or prospectively. Retrospective studies frequently are conducted on rare diseases or conditions to determine a common factor in the past that can be associated with that disease or condition. Retrospective studies rely on medical records or subject recall, both of which have drawbacks because information can be missing or forgotten. Prospective studies are preferred for determining cause-and-effect relationships because they can be controlled for bias.

Observational studies, such as case reports or case series, cohort, case-control, and cross-sectional studies, are not interventional and usually are conducted to observe the prevalence or incidence of an event or factor. Case reports or case series are observations related to a particular drug or disease in one patient or a group of patients. These types of reports are retrospective and do not involve any type of randomization or blinding. Case reports and case series are useful for describing rare disorders, adverse effects, or teratogenic effects. Cohort studies involve a group or cohort of patients with exposure to a factor (e.g., taking a drug) who are followed prospectively and observed for the

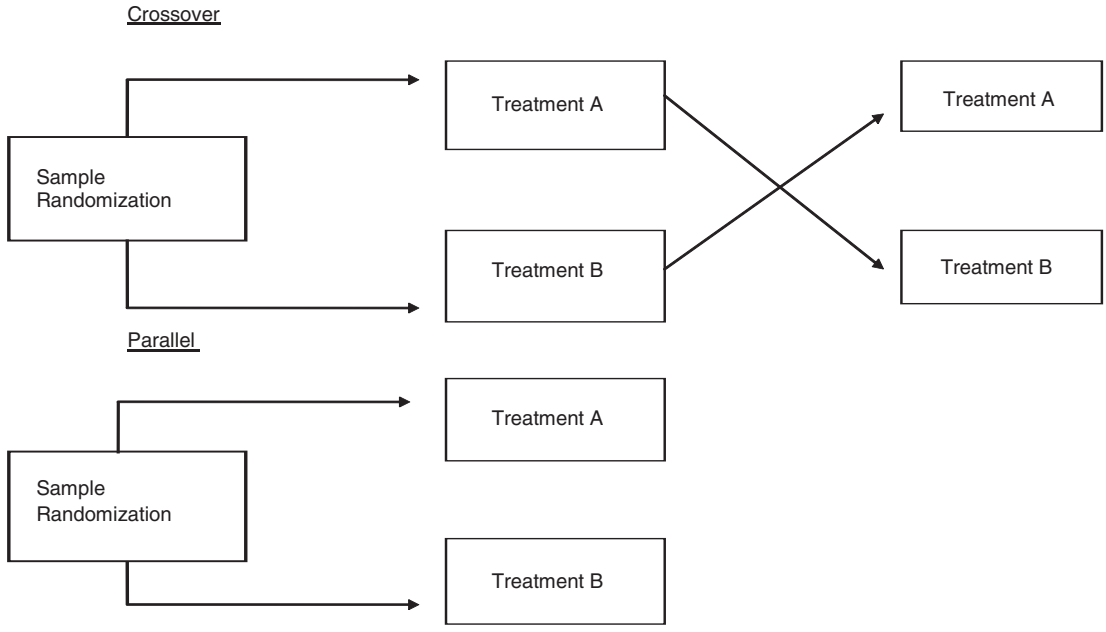

Figure 1-1. Crossover and parallel study design.

development of an outcome. Cohort studies also can be conducted retrospectively if accurate records are available. Cohort studies also are called follow-up studies because the patients are followed over time. These patients are compared to another group that was not exposed to the factor to determine if exposure to the factor is associated with development of the outcome or disease. Cohort studies frequently are used to determine if a new drug results in any rare adverse effects that were not detected in clinical trials. Disadvantages of cohort studies are that they can be expensive to conduct, time-consuming, highly subject to attrition, and require a large patient population. Cohort studies also are susceptible to confounding variables. A recent example of a cohort study was published in the Journal of the American Medical Association that described the association between vaccination with a thimerosal-containing vaccine and the development of autism. Children vaccinated with a thimerosal-containing vaccine were compared to those vaccinated with a thimerosal-free vaccine. A total of 467,450 children were included in the cohort are and were followed through age 11 or until December 31, 2000. Four hundred seven cases of autism and 751 cases of autistic disorders were identified in children who received at least one dose of whole cell pertussis vaccine. Of the 407 cases of autism, 303 received thimerosal-free vaccine and 104 received thimerosal-containing vaccine; of the 751 cases of autistic disorder, 430 received thimerosal-free vaccine and 321 received thimerosal-containing vaccine. No causal relationship was found between vaccination with thimerosal-containing vaccines and development of autism (relative risk = 0.85 [95% confidence interval = 0.60–1.20]).

Case-control studies are similar to cohort studies except that they are always retrospective. Case-control studies are conducted to determine if a particular clinical effect is related to an exposure to a drug or other factors. These studies compare patients with a disease (cases) to those without the disease (controls) to identify if the cases had an exposure that caused the disease. This type of trial is best suited for the study of rare diseases or those diseases that take a long time to develop. For example, a recent case-control study published in the Journal of the American Medical Association compared the duration and type of combined hormone replacement therapy use in 975 women with breast cancer to 1007 women without breast cancer. Patients who had ever used combined hormone replacement therapy were found to have a 1.7-fold (95% confidence interval = 1.3–2.2) increased risk for breast cancer. The risk was significant regardless of the progestin regimen used. Disadvantages of this type of study design include the reliance on patient recall and appropriate selection of a control group. The control group should have equal exposure to all external factors that could affect the results except for the variable being investigated. For example, controls drawn from an ambulatory population will be exposed to different risk factors than a hospitalized population. Investigators often match cases to controls to ensure that each case has a control with similar characteristics; however, determining which characteristics to match is difficult because variables that are related to the disease under investigation should not be matched. Recall bias is even more prevalent in case-control trials because patients with a disease often are more likely to recall general events in the past than patients without a disease. Advantages associated with case-control studies include lower cost to complete, fewer patients required, and less time-consuming to conduct.

Cross-sectional studies survey the characteristics of a population at a given time and are particularly useful for measuring the prevalence of a disease or event. Prevalence is defined as the number of individuals with a disease at a given time divided by the population at risk for the disease at that time. Prevalence is different from incidence which is defined as the number of new cases of a disease that occur in a given time interval divided by the population at risk at the beginning of the time interval. Incidence is always expressed in terms of a unit of time. A cause-and-effect relationship cannot be determined from a cross-sectional study. To determine the prevalence of angiotensin-converting enzyme inhibitor use in patients with heart failure, a cross-sectional study could be conducted. This study would provide the investigator with the prevalence of angiotensin-converting enzyme inhibitor use in this population but would not be able to associate angiotensin-converting enzyme inhibitor use with a clinical effect. Transient effects or biases are possible with cross-sectional studies because they only measure the prevalence at a single point in time.

Meta-analysis

Meta-analysis is a type of systematic review that involves a thorough review of the published literature on a particular question and includes a statistical analysis of the pooled results. Meta-analyses are used to answer a question that could not be answered with previous research. Specifically, meta-analysis can be useful when previous studies for the outcome of interest did not have adequate power to detect a difference. The main reason to conduct a meta-analysis is to increase sample size and decrease the chance for type II error. In addition, meta-analyses are capable of generating a hypothesis to be tested in a large clinical trial and in calculating the sample size required to detect a difference between treatment groups. The Cochrane Collaboration is an international group of health care professionals and epidemiologists that on a continual basis prepare, maintain, and disseminate meta-analyses. More information about this group can be found at *http://www.cochrane.org*.

Many concerns have been raised regarding meta-analysis that have led to questions about their role in developing treatment guidelines and guiding decision-making about patient care. One of the most obvious problems with

Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA 2003;290:1763–6.

Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 2003;289:3254–63.

combining data from several different studies is that biases and limitations of each individual trial also are combined. In addition, new sources of bias can arise through the methodology of the review and the studies included in the review. Investigators conducting meta-analyses must be diligent in their search for articles to include in their analyses because articles with positive results are more likely to be published (publication bias) than those with negative results. Investigators must attempt to identify all articles published on a topic through the use of multiple databases and reference lists. Investigators also need to address the homogeneity of the studies included in the analysis because they need to be similar enough to combine the results. If the studies included are too heterogeneous then the results of the meta-analysis may not be applicable to the target population. The homogeneity of the meta-analysis also should be addressed statistically to determine if the differences among the included studies are because of chance. Investigators need to state clearly the search strategy used, the inclusion and exclusion criteria, they need to explain why trials were excluded from the analysis, and complete a thorough sensitivity analysis. Results of a meta-analysis can be reversed when an adequately powered randomized, controlled trial is published. The reader should refer to the Understanding Statistics: An Approach for the Clinician chapter for more information on meta-analysis.

Randomized, controlled trials are considered the gold standard for comparing two or more drugs and to establish a cause-and-effect relationship. They are prospective and can control for confounding variables by patients being randomly assigned and/or by use of stratification. The disadvantages of randomized, controlled trials include their cost and time constraints. The structure of randomized, controlled trials is discussed in more detail in the next section.

Consolidated Standards of Reporting Trials Statement

The Consolidated Standards of Reporting Trials Statement, initially published in 1996 and subsequently updated in 2000, was created to improve and standardize the reporting of randomized, controlled trials in the literature and to help facilitate literature evaluation. The Consolidated Standards of Reporting Trials statement includes a list of items that should be addressed in all randomized, controlled trials and a flow diagram for documenting the patients at each stage of the trial (see Table 1-5 and Figure 1-2). The Journal of the American Medical Association and Lancet have endorsed the Consolidated Standards of Reporting Trials statement and refer to it in their information for authors. A complete list of the journals that have endorsed the Consolidated Standards of Reporting Trials statement is available at *http://www.consort-statement.org/endorsements/journals/journals.html*.

Structure of a Randomized, Controlled Trial

The Title section highlights the components of a randomized, controlled trial with an emphasis on its critical appraisal. Title, author affiliations, abstract, introduction, methods, results, discussion, references, and sponsorship are discussed in their own sections.

Title

The title and authors sections are important to review when analyzing an article. Although the title of an article should reveal the purpose of the study, it should not allow readers to draw any conclusions about the results. The title should contain enough information so the reader can decide if the article is relevant to their practice. The title should not reveal the results of the study because this can bias the reader before he or she reads and interprets the methods and results. Compare these two example titles:

- The safety and efficacy of amoxicillin and cephalexin for treating acute otitis media.
- Amoxicillin is superior to cephalexin for treating acute otitis media.

The first title is preferred because it is unbiased; it neither reveals the results of the study, nor makes conclusions about the study.

Now compare the previous example to this example:

- A comparison of two antibiotics for treating pediatric infections.

This title, although not biased, does not provide the reader with enough information to decide whether to read the entire article.

Author Affiliations

The authors' affiliations are an important section of the article to review to ensure that the authors are competent and free of bias. The reader can ascertain the competency of the authors by reviewing their credentials and affiliations. The authors' affiliations also can reveal any potential for bias, especially if any of the authors are affiliated with a pharmaceutical company (see the References and Sponsorship section). Many clinical trials include statisticians as part of the group, which can improve the quality of the article. The institutions involved in the study often are indicated with the description of the author's credentials and is important to note when evaluating the external validity of the trial. The results of studies conducted at small institutions may not be applicable to larger institutions.

Abstract

The abstract serves as a summary of the article and typically is 250 words in length or less. The purpose of an abstract is to provide the reader with sufficient information to decide if it is worthwhile to retrieve the entire article. The abstract should cover the purpose of the study, study design, methods, results, and conclusion. Many journals use structured formats for abstracts that summarize the most important sections of the article: hypothesis, setting, objectives, methods, results, and conclusions. Although the abstract is a quick way to learn what a study is about, it does not substitute for reading the entire article. Abstracts often are written by the author and, therefore, can be subject to bias. Because of space limitations for the abstracts, the methods of the study cannot be discussed adequately and flaws cannot be detected. Table 1-6 lists the content of a structured abstract.

Table 1-5. CONSORT Checklist for Randomized, Controlled Trials

PAPER SECTION and topic	Item	Description	Reported on page No.
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned")	
INTRODUCTION Background	2	Scientific background and explanation of rationale	
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	
Objectives	5	Specific objectives and hypotheses	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations and training of assessors)	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	
Randomization — Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking and stratification)	
Randomization — Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned	
Randomization — Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	
Blinding (masking)	11	Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons	
Recruitment	14	Dates defining the periods of recruitment and follow-up	
Baseline data	15	Baseline demographic and clinical characteristics of each group	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%)	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval)	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory	
Adverse events	19	All important adverse events or side effects in each intervention group	
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes	
Generalizability	21	Generalizability (external validity) of the trial findings	
Overall evidence	22	General interpretation of the results in the context of current evidence	

CONSORT = Consolidated Standards of Reporting Trials.
Available at *www.consort-statement.org/statement/revisedstatement.htm#flow*. Accessed November 8, 2004.

Introduction

The introduction of an article provides the reader with background information related to the question addressed and explains the rationale for completing the study. The reader already should understand what standard treatments are, the limitations of current treatments, and why the treatment to be studied might offer potential advantages. The most important part of the introduction is the study objective. This typically is in the last paragraph of the introduction and will identify the specific question to be answered. The rest of the paper should follow from the study's objective with the methods, results, and conclusion all directed toward answering this question. A good study objective should explain what is going to be tested, why is it being tested, who will be tested, and how will the tests be conducted. For example, the objective of an article on asthma stated: "The objectives of this study were to evaluate the efficacy of desloratadine compared with placebo and montelukast (an established asthma treatment) in improving measures of asthma, including total and individual asthma symptom scores, forced expiratory volume in 1 second, peak flow measurements, and the need for bronchodilator rescue drugs in patients with concurrent asthma and seasonal allergic rhinitis." A poorly written objective for this same study would have been: "The use of desloratadine and montelukast was studied in asthma patients." This latter statement does not describe how the efficacy will be determined and it does not completely describe the patient population. A poorly written objective makes it difficult to evaluate an article because the reader does not clearly understand the authors' purpose. The objective also is used to develop the null and alternative hypotheses of the clinical trial that are used for the statistical analyses. The null hypothesis states that no difference exists between the treatment groups and the alternative hypothesis states that there is a difference between the treatment groups.

Table 1-6. Content of a Structured Abstract

Context—rationale for the study
Objective—main objective for the study and hypothesis
Design—should describe the type of trial (e.g., randomized, controlled, double-blind, parallel trial) and length of follow-up
Setting—inpatient/outpatient, general community practice, or university-affiliated institution
Participants—key characteristics of patients or study participants; includes a description of how participants were selected and the number of patients who discontinued because of adverse drug reactions
Interventions—details of intervention including the drug name, dose, and duration of therapy
Main outcome measures—primary and secondary outcome(s)
Results—major results should be summarized with confidence intervals and level of significance (p value) as appropriate
Conclusions—should be based on evidence and contain a statement regarding clinical relevance; this must not be too broad or overgeneralized (external validity) and should indicate if further data are needed

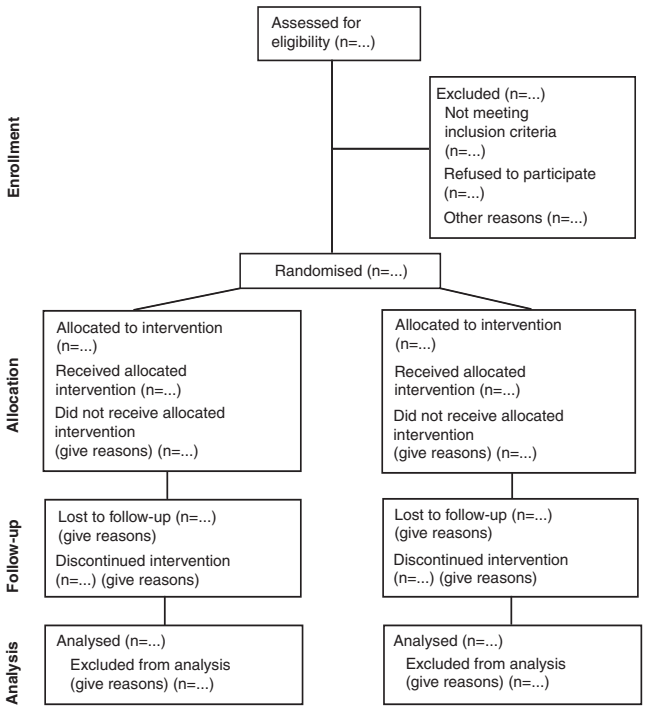

Figure 1-2. Revised template of the CONSORT diagram showing the flow of participants through each stage of a randomized trial.
CONSORT = Consolidated Standards of Reporting Trials.
Available at *www.consort-statement.org/statement/revisedstatement.htm#flow*. Accessed November 8, 2004.

Methods

Although the methods section of an article is the most important section to understand and evaluate, it all too frequently is skipped by the reader. Typically, the methods section describes the study design, the inclusion and exclusion criteria, interventions and controls, sample size, blinding techniques, randomization procedures, the outcome measures used, and statistical tests. Analysis of the methods section is the primary tool by which to determine the validity of the results. This section should be discussed in enough detail that the study results could be duplicated. Authors of many large studies prepublish their methods in another article. However, it is important always to read the entire methods section of a clinical trial even if that means retrieving an additional article.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria define the study population. They should be clearly and completely stated so readers can determine if the study results can be extrapolated to their own patient population. Inclusion criteria are a list of characteristics that patients must have to be enrolled in the study. The inclusion criteria should specify how the patients were diagnosed with the disease to precisely define the patient population. Exclusion criteria are characteristics that will preclude a patient from enrollment in the study. These serve to provide a homogenous study sample and ensure patient safety by excluding those who could potentially be harmed.

Exclusion criteria must be balanced between being too restrictive and not restrictive enough. If the exclusion criteria are too restrictive, it may be next to impossible to apply the results to most patient populations. However, if the exclusion criteria are not restrictive enough, certain patient groups could confound the results. For example, because corticosteroids are known to put patients at increased risk for the development of osteoporosis, not excluding patients taking corticosteroids in a trial on osteoporosis could confound the results.

Interventions and Controls

The interventions used in the study need to be discussed thoroughly, including the drug(s), dose, route, duration, and a description of any placebo used. Controls are used in clinical trials to "control" for any confounding factors that could affect the results, such as the extensive monitoring that usually occurs in clinical trials or the natural course of the disease. Placebo controls and active controls are the two most frequent types used. In a placebo-controlled trial, the control group receives a placebo that should be identical to the study drug in terms of appearance, color, odor, route, and taste. Placebo-controlled studies allow the investigator to ascertain the absolute effect of the drug being studied. Placebo-controlled studies control for the psychological aspects of enrollment in a clinical trial and, therefore, are the best method for determining if a drug is effective. In an active-controlled trial, the control group usually receives the current gold standard of treatment. This method is used when it would be unethical for patients not to receive active treatment, such as in a study of infectious diseases. Active controls also are used when investigators want to compare the safety and efficacy of a new treatment to an existing one. An important consideration in active-control trials is whether the drugs were titrated to patient response or if a fixed-dosage regimen was used. Titrated schedules frequently are used in diseases where significant interpatient variability in response occurs, such as hypertension or asthma. The doses used for the intervention and active controls should be evaluated to ensure that therapeutic doses of both were used. In addition, titration schedules should be clearly stated *a priori*.

Historical controls also are used in some clinical trials to compare the results with a previously conducted trial. Historical controls often are used when it would be unethical to use a placebo or active control. These studies use data that were collected before the new intervention or treatment became available. One example is the first study conducted on the use of lepirudin for anticoagulation in patients with heparin-induced thrombocytopenia. In this case, it would be unethical to withhold this new treatment and there was no active alternative treatment; therefore, investigators compared outcomes to a historical control group of patients who had the condition before the development of the new drug. Another example is the implementation of a clinical service where the results of the new service are compared to what had been in place previously. The advantage of using historical controls is that they often are readily accessible; however, they also rely heavily on either medical records or subject recall and, therefore, often provide incomplete data. In addition, the use of historical controls can confound the results because there could be differences in quality of care between the different time periods.

Outcome Measures

Investigators need to clearly define all outcome measures before initiation of the study to avoid fishing for significant results after the study is completed. The primary outcome measure is the most important efficacy parameter as predetermined by the authors. This outcome measure is used to determine sample size. Most trials have only one primary outcome measure because the use of multiple primary outcome measures increases the chance for type I error or falsely concluding that results are significant. Secondary outcomes frequently are used in clinical trials to examine other outcomes of interest. One problem commonly encountered in clinical trials is a lack of standardization of the methods used to evaluate the primary outcome. It is recommended that previously validated tools or assessment scales be used for outcome assessment to allow for comparisons between similar trials. For example, the International Headache Society has published a guideline to improve the quality of clinical trials on migraines. Within these guidelines, specific recommendations are made with respect to how to evaluate the results and which scales are appropriate to use.

Randomization

Randomization is unique to clinical trials because allocation to treatment group is predetermined in all other study types. Randomization ensures that all patients enrolled have an equal chance of being assigned to any of the treatment groups. This method improves the likelihood that baseline characteristics (clinical and socioeconomic factors) of the groups are similar, eliminates bias that could be introduced if the investigators assigned the patients to treatment groups, and requires most statistical analyses; however, randomization cannot eliminate the risk for confounding variables. One analysis of clinical trials reported that nonrandomized studies tend to overestimate treatment effect.

Two general types of randomization exist: simple and restricted. Simple randomization is based on a sequence of random assignments and includes the use of random number tables or computer-generated models. Restricted randomization is used to ensure balance between the groups for a certain characteristic or for size. Two types of restricted randomization are block randomization and stratification. Block randomization is used to ensure equal numbers of patients in the study groups and stratification is used to ensure the study groups are well matched for certain

Greinacher A, Volpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. Circulation 1999;99:73–80.

Tfelt-Hansen P, Block G, Dahlof C, et al. Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia 2000;20:765–86.

characteristics. Some methods used for treatment assignment that are not considered appropriate include the use of phone numbers, admission numbers, alphabetical lists, date of birth, or alternating treatments based on enrollment sequence. These methods can introduce bias either by the investigator or because of the systematic nature of the method used. In addition to explaining the method used for randomization, authors should explain how investigators were kept blind to the randomization process. Randomization should not be confused with random sampling. Random sampling is the procedure done to ensure that the sample of patients chosen for the study is representative of the population. There are many methods of sampling, including simple random sampling, systematic sampling, stratified sampling, cluster sampling, and nonprobability sampling.

Blinding

Blinding commonly is incorporated into clinical trials to avoid bias. All studies that involve subjective responses or in which bias could be introduced if investigators were aware of treatment assignment must be blinded. Everyone involved in a clinical trial has an opinion about the treatment being investigated. Although blinding can be expensive and time-consuming, it is necessary to prevent these opinions from affecting the study results. There are three types of blinding: single, double, and triple. In single-blind studies, either the investigator or the patient is blind to the treatment assignment. In double-blind studies, both the investigator and the patients are blind to their assigned treatment. In a triple-blind study, the investigators, patients, and the group who analyzes or evaluates any data are unaware of the treatment assignment. Triple-blind studies often are used when specific diagnostic tests must be interpreted. Additional groups involved in clinical trials that should be blinded include pharmacy and data entry personnel. One important aspect involved in the blinding process involves administration of the drug. Readers should check if the author or investigator ensured that treatment and control dosage forms were made to look identical and administered at the same frequency. In studies involving different dosage forms, multiple placebos are required to maintain blinding. An example would be a study comparing a nebulized solution to tablets. In this case, one treatment group should receive an active nebulized solution and a placebo tablet and the other treatment group should receive a placebo nebulized solution and an active tablet. This design is called double-dummy. Blinding can be challenging if one of the active treatments has a unique side effect. In this case, additional measures should be taken to limit investigator access to this information during the trial, or it may be necessary to evaluate from outside the institution.

Statistics

The statistical methods of the trial should be described clearly for the reader to assess the appropriateness of the tests chosen. The reader should possess a basic knowledge of biostatistics that allows the results to be interpreted and the appropriateness of the chosen statistical methods to be evaluated. The main concepts of statistical analyses are reviewed; however, the reader is referred to the Understanding Statistics: An Approach for the Clinician chapter for further information on this subject. As previously discussed, the null hypothesis states there is no difference between the treatment groups and the alternative hypothesis states that a difference exists. There are two types of errors that occur with hypothesis testing: type I and type II error. Type I errors occur when the authors state that there is a difference between the treatment groups (reject null hypothesis), when in fact there is no difference. Type II errors occur when the authors state that there is no difference between the treatment groups (retain null hypothesis), when in fact there is a difference. Type I errors are considered to be worse than type II errors and, therefore, the threshold for type I error is lower than that for type II error. The α value determines the magnitude of type I error the authors are willing to accept and commonly is set at 0.05 or 5%. This means that a type I error concluding there is a difference between treatments when no difference exits will occur five times out of 100 (5%). The statistical analyses will report p values, which determine the statistical significance of the results. Any p values that are less than the set α value are considered to be statistically significant. The β value determines the amount of type II error that the authors are willing to accept and commonly is set at 0.1 or 0.2 (10–20%). The power of a study is 1-β or commonly 80–90%.

Sample Size

Sample size is one of the most important variables for readers to critique when reading the methods section of a clinical trial, particularly when the study results are inconclusive. Investigators need to explain how the sample size was determined. This is called the power analysis. Four factors need to be defined to conduct a power analysis: β , α, the expected difference between the groups, and the variation or standard deviation. These four variables determine how many patients are required to detect a difference between the groups. Please refer to the Understanding Statistics: An Approach for the Clinician chapter for more detailed information on this topic. Authors should state the calculated sample size in the methods section of the article. The reader needs to look critically at the number of patients who were analyzed for efficacy in the results to ensure there were enough to detect a difference. If patients dropped out of the study, resulting in fewer than that required by the power analysis, then the possibility of type II error must be considered if the results showed no difference between the groups. If a difference was observed between the groups, then there were enough patients to detect a difference; however, a small sample size can result in overestimation of the treatment effect because of outliers. Large samples can result in statistically significant results that are not clinically significant; therefore, authors often will define a clinically significant response.

Interim Analysis

An interim analysis occurs when an investigator evaluates the data at specific time points before the end of the study. This typically is done when the results of the study could have a significant clinical impact on the current standard of care or if the safety of the participants could be

compromised. If the data show that one of the treatments has a significant benefit or causes significant harm, the trial can be stopped early. If interim analyses are going to be performed, the investigators need to describe this *a priori* in their methods section along with the statistical methods used to control for the multiple analyses and the stopping rules that will be applied. A classic example of interim analyses was in the AIDS Clinical Trials Group Protocol 076 which evaluated the use of zidovudine to prevent human immunodeficiency virus transmission from mothers to their infants. This trial found a 67.5% relative risk reduction for the transmission of human immunodeficiency virus from mothers to infants in the group treated with zidovudine at the first interim analyses; therefore, the trial was stopped early.

Intention-to-Treat Analysis

The investigators should state if an intention-to-treat analysis was conducted. In an intention-to-treat analysis, all of the patients who were randomized to treatment are included in the data analyses regardless of whether they received their assigned treatment for the entire study. The last observation carried forward method commonly is used to account for patients who drop out of the study. This method allows investigators to use the last measurement observed for a patient to be carried through the remainder of the trial. Intention-to-treat analyses are promoted by the Food and Drug Administration because they provide a more conservative analysis of the drug's efficacy. Intention-to-treat analysis is in contrast to a per-protocol analysis where only the patients who received the treatment and followed the protocol were analyzed. In this analysis, patients who could not tolerate the treatment or did not benefit from the treatment may drop out of the study, not be included in the analysis, and bias the results.

Results

The results section of a clinical trial should present the baseline characteristics of the patient population and the measured outcomes, including numbers and statistical significance. The main points to consider when evaluating the results section include baseline characteristics, clarity of data presented, intention to treat, sample size, and adverse events. Table 1-7 lists criteria for evaluating the results section of an article.

Baseline Characteristics

The baseline characteristics commonly are presented in the first table in the results section. These data should be presented as means and standard deviations for all continuous variables. In addition, ordinal data (ordered groups) that are not normally distributed, should not be summarized using means and standard deviations but should be presented by medians with a range or interquartile range. The use of standard errors typically is not recommended for baseline characteristics. The baseline characteristics serve two main purposes: 1) they give a detailed picture of the patient population that was included in the study, and 2) they allow the reader to compare the characteristics of the patient groups if they are balanced. Statistical analyses often are conducted on the baseline characteristics to verify that the groups were equivalent at baseline; however, this is a questionable practice because any differences at baseline are because of chance as long as randomization was properly conducted. The Consolidated Standards of Reporting Trials statement indicates that the use of significance tests on baseline differences is inappropriate. Randomization cannot guarantee balance of baseline characteristics, and baseline differences should be viewed as potential confounders. Readers need to analyze the baseline characteristics table to identify any potential confounding factors that were not controlled for and to determine if the study population is similar to the population to which the results are to be applied.

Table 1-7. Questions for Evaluating the Results Section

Were all patients accounted for?
Were the patients' baseline characteristics comparable between the two groups at baseline?
Were the results for all primary and secondary outcomes clearly presented?
Was an intention-to-treat analysis conducted?
Did the study meet the sample size requirement?
Were confidence intervals provided?
Are adverse events reported?
Could type I or type II errors have occurred?

Flow Diagram

The results section of an article should contain a flow diagram to demonstrate the number of patients at each stage of the study (see Figure 1-2). Every patient who was randomized to treatment needs to be accounted for in the results. The authors need to specify the number of patients who were assigned to each treatment group, received the treatment, dropped out of the study, completed the protocol, and were analyzed for the primary outcome. The authors also need to explain why patients were excluded or dropped out of the study. This allows the reader to understand if the patients could not tolerate the drugs, if they were lost to follow-up, or if the investigators excluded them. These various reasons can affect the internal and external validity of the trial.

Data and 95% Confidence Intervals

The results for each primary and secondary outcome should be presented as a summary of the effect and an estimate of the precision. This commonly is seen as a mean and 95% confidence interval. Relative risk, odds ratio, and hazard ratios also are used when the use of a mean is not appropriate. The 95% confidence interval has become more common in recent years. The 95% confidence interval gives the reader a range of numbers that will contain the true population parameter 95% of the time if the experiment was repeated on the entire population. The use of 95% confidence intervals also allows the reader to infer both the statistical and clinical significance of the results. The reader is referred to the Understanding Statistics: An Approach for the Clinician chapter for more detail on this topic. The results section also should contain a summary of the adverse events that occurred in the trial and their frequency.

Table 1-8. Topics Contained in the Discussion Section

Summary of the important results
Explanation of the mechanism behind the results (especially unexpected results)
Comparison of the results to other published trials (positive and negative)
Limitations of the study
Discussion of the clinical implications and generalizability (external validity) of the results

Discussion

The discussion section of a clinical trial usually is where the authors can elaborate on the importance of their findings. Many journals have attempted to structure the discussion sections to improve their consistency. Table 1-8 lists the topics that should be addressed in the discussion section. The reader should be suspicious of any biased language, such as "clearly superior" or "trend toward significant", in the discussion section. In addition, readers should be cautious of any conclusions drawn from a post hoc subgroup analysis. This topic is further addressed in the Understanding Statistics: An Approach for the Clinician chapter.

References and Sponsorship

The reference section of a primary literature article is where the authors list every article that was referenced in the text. These articles provide documentation for the data that was presented to support the current study. One commonly used format for referencing is the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (available at *http://www.icmje.org*). Another format used is the American Medical Association's Manual of Style, which is included in the Annotated Bibliography for this chapter. Most primary literature articles have a section to describe the source of funding for the trial. This section conveys the name of the study sponsor as well as a description of the participation of the sponsor. Potential conflicts of interest for the study authors also may be disclosed. The reader should be aware of the potential for bias involving conflict of interest and funding; however, bias does not always exist in studies sponsored by pharmaceutical companies. The affiliations of the authors and the role of the study sponsor must be evaluated. Less bias may exist if the study sponsor only played a minor role in the conduct of the study (e.g., supplied the drugs) than if the sponsor was involved directly in the conduct of the study (e.g., statistical analysis).

The Publication Process

Steps

The process of preparing a manuscript for publication usually is referred to as the publication process. There are many steps in the publication process, including selection of a journal, preparation for submission, review/peer review, revision(s), and resubmission. Manuscripts submitted to a journal for publication will undergo a standardized review process, which often includes peer review. After a manuscript is received by a journal, it first undergoes review by the editor in chief to determine its appropriateness for publication in the journal. If the manuscript is considered appropriate for publication, it is then sent for peer review.

Peer Review

One of the most important steps in the publication process is peer review. Peer review typically is defined as a review by experts who are selected by the editor of the journal. Peer review serves many important purposes. The peer-review process helps the editor to select manuscripts for publication based on importance and clinical relevance and that are expected to contribute to the quality of medical care and research. Characteristics reviewers should consider when evaluating the importance of the work include scientific advancement, clinical relevance, newness of information, and overall interest to general readership. Aspects that affect the quality of a manuscript include appropriate study design and methods, adequate description of research hypothesis and methods, thorough data analysis, appropriate conclusions based on results reported, and ethics of the study. Peer review provides the editor with an evaluation of the manuscript and an opinion on the timeliness, internal and external validity, and potential clinical importance of the material. The peer reviewer will make a recommendation of whether a manuscript is acceptable for publication. Peer-reviewed journals are considered to be of higher quality because the articles undergo such a rigorous review. However, some peer-reviewed journals may publish supplements that are not peer reviewed. Journals typically will note that they are peer reviewed on the page that lists the editorial board or in the information for authors. Examples of peer-reviewed journals include Annals of Pharmacotherapy, Pharmacotherapy, American Journal of Health-Systems Pharmacy, New England Journal of Medicine, and Annals of Internal Medicine. Drug Topics and Pharmacy Times are not peer reviewed and this information usually is stated in the information for authors.

Reasons for Revision

After peer review, the editor decides if the manuscript should be accepted or if an additional review is needed, which may include a review of the statistics. If the manuscript is not rejected, it is returned to authors for revision. Revisions required of a manuscript can vary and may depend on the status and quality of the journal. For example, research papers with methodological flaws that cannot be corrected (usually because the study has already been completed) may be difficult to get published. A study in the Journal of the American Medical Association investigated the types of changes found necessary in manuscripts submitted to the Annals of Internal Medicine. Besides corrections in spelling, grammar, and style, five major reasons for changes to manuscripts were identified: too much information, too little information, inaccurate information, misplaced information, or structural problems. Missing or unnecessary information was the most frequent cause for revision. Once a manuscript is revised, a final decision on whether to accept the manuscript for publication is made by the editor.

Purcell G, Donovan S, Davidoff F. Changes to manuscripts during the editorial process. JAMA 1998;280:227–8.

Fate of Rejected Articles

Manuscripts that are rejected by one journal may be published by another journal. The fate of manuscripts rejected by the Annals of Internal Medicine was analyzed. During 1993 and 1994, 3552 manuscripts were submitted to the journal, 3180 of which were rejected. The authors took a random sample of 350 of these rejected manuscripts and determined their publication fate. A total of 240 (69%) of these manuscripts eventually were published elsewhere, mostly in specialty journals. The average time from rejection to subsequent publication in these other journals was 18 months. The authors also found that the journal in which the manuscript eventually was published had a lower impact factor than the Annals of Internal Medicine. The impact factor is a measure of how frequently an average article in a journal is cited in a year. This factor is one indicator of a journal's relative importance by quantifying how frequently it is used by other authors. The impact factor of a journal is calculated by dividing the total number of current citations to articles published in the previous 2 years by the total number of articles published during that 2-year period. For example, if a journal publishes 300 articles during 2002 and 2003 and these articles are cited 3000 times, then the impact factor is 10. The impact factor can be deceiving if the journal has a narrow audience, such as Archives of Family Medicine (impact factor 2.878).

Another measure of a journal's importance is the immediacy index—how quickly an average article is cited. A high immediacy index suggests that the journal publishes articles on new or innovative research. Information on the impact factor and immediacy index of a journal is available from ISI Journal Citation Reports (*http://isi4.isiknowledge.com/*). Based on impact factor, New England Journal of Medicine, Journal of the American Medical Association, Lancet, Annals of Internal Medicine, and Annual Review of Medicine are the top five general and internal medicine journals in 2002 out of more than 100 journals rated. In 2002, the New England Journal of Medicine had the highest impact factor of 31.736 and had the highest immediacy index of 8.318.

The Internet

The use of the Internet has exploded during the past several years. It is estimated that more than 100,000 Web sites contain health-related information and that almost 100 million Americans search the Internet for health care information. The main limitation that arises with the use of the Internet is quality of the available information. Several studies have been conducted to evaluate the quality of medical information on the Internet. One study was conducted to determine if important drug safety information was mentioned on top Internet sites. Top Internet sites were the first 10 sites that were identified with major search engines. The Food and Drug Administration recently released a total of 20 warnings on severe adverse effects for 21 different drugs. Some examples of the warnings researched were hemorrhagic stroke with phenylpropanolamine and fatal rhabdomyolysis with cerivastatin. A total of 519 Web sites related to these 21 drugs were located through the use of seven different search engines. Only 31.8% of these Web sites mentioned the Food and Drug Administration warnings. Web sites that did not contain an author or date were least likely to contain the warnings. The safety information was more likely to be found on Web sites that were oriented toward physicians, for drugs withdrawn from the market, and when no other adverse effects were noted for the affected organ system. Another study was conducted to evaluate the accuracy of information available on the Internet related to the use of mifepristone (RU 486) for abortion. An Internet search identified 40 Web sites that contained patient-oriented information on mifepristone. Of the 40 sites, 15 (37.5%) were in favor of its use, 16 (40%) were against its use, and nine (22.5%) were neutral. Incorrect information was identified in 12 Web sites and was significantly more common in Web sites opposed to the use of mifepristone than in those that favored it (56.3% vs. 6.7%; $p<0.006$). Examples of incorrect information included misinterpretation of Food and Drug Administration statements, inaccurate summaries of clinical trial results, and false claims regarding the effects of the drug. In addition, Web sites that were opposed to the use of mifepristone had significantly fewer links to other Web sites and significantly more graphic descriptions.

How to Evaluate a Web Site

In response to concerns about the quality of information on the Internet, several groups have developed codes of conduct or rating systems that are used to rate the quality of a Web site. The main points to consider when evaluating a Web site include author credentials, use of an advisory board, references within the document, sponsorship, and timeliness. Table 1-9 summarizes the factors to consider when assessing the quality of content on a Web site.

Health on the Net Foundation Code of Conduct

One of the first organizations to develop a code for evaluating health care Web sites is the Health on the Net

Table 1-9. Evaluating the Quality of a Web Site

Authorship of the content, including credentials
Use of an advisory board
References for the clinical content
Disclosure of funding or sponsorship
Timeliness of the information
Seal of approval or quality label

Ray J, Berkwits M, Davidoff F. The fate of manuscripts rejected by a general medical journal. Am J Med 2000;109:131–5.

Tatsioni A, Gerasi E, Charitidou E, Simou N, Mavreas V, Ioannidis JP. Important drug safety information on the Internet: assessing its accuracy and reliability. Drug Saf 2003;26:519–27.

Mashiach R, Seidman GI, Seidman DS. Use of mifepristone as an example of conflicting and misleading medical information on the internet. BJOG 2002;109:437–42.

Foundation (*www.hon.ch*). In 1996, the Health on the Net Foundation developed a list of principles that was intended to improve the quality and reliability of information on health care Web sites. Submission of a Web site to Health on the Net Foundation is voluntary; if a Web site abides by the Health on the Net Foundation code, it is allowed to display the Health on the Net Foundation logo. About 3000 Web sites currently display the Health on the Net Foundation logo. Table 1-10 summarizes the principles of the Health on the Net Foundation code. Other organizations involved in developing criteria for the evaluation of heath-related Web sites include the Internet Health Coalition (*www.ihealthcoalition.org*) and Health Internet Ethics (*www.hiethics.com*).

Useful Web Sites

Most clinicians use the Internet as a resource today because of its widespread availability and ease of access. The Internet is a valuable resource when trying to find recently released information. In addition, most drug companies have Web sites that are kept up-to-date with drug approvals and contain package inserts for most drugs. There are many Web sites that health care providers find useful in their clinical practice. Table 1-11 contains a list of Web sites that are used commonly.

Conclusions

All pharmacists need to evaluate the literature to answer questions that arise in their practice, especially considering the number of drug approvals each year. Pharmacists need to use a systematic approach when trying to answer these questions to be sure that their search is efficient and complete. Many of the questions posed to a pharmacist require the use of the primary literature; therefore, literature evaluation skills are necessary. Pharmacists must be able to read a clinical trial and identify the flaws that might limit their ability to apply the results to their clinical practice. One phrase frequently heard at journal clubs is "keep it or toss it" and this question can only be answered after a thorough evaluation of the article. The Consolidated Standards of Reporting Trials statement is an excellent tool for pharmacists to refer to when evaluating a clinical trial to identify errors or missing information.

Table 1-10. HON Code of Conduct for Medical and Health Web Sites

Principle	Description
Authority	Any medical or health advice provided and hosted on this site will only be given by medically trained and qualified professionals unless a clear statement is made that a piece of advice offered is from a nonmedically qualified individual or organization.
Complementarity	The information provided on this site is designed to support, not replace, the relationship that exists between a patient/site visitor and his or her existing physician.
Confidentiality	Confidentiality of data relating to individual patients and visitors to a medical/health Web site, including their identity, is respected by this Web site. The Web site owners undertake to honor or exceed the legal requirements of medical/health information privacy that apply in the country and state where the Web site and mirror sites are located.
Attribution	Where appropriate, information contained on this site will be supported by clear references to source data and, where possible, have specific HTML links to that data. The date when a clinical page was last modified will be clearly displayed (e.g., at the bottom of the page).
Justifiability	Any claims relating to the benefits/performance of a specific treatment, commercial product, or service will be supported by appropriate, balanced evidence in the manner outlined in the Attribution Principle.
Transparency of Authorship	The designers of this Web site will seek to provide information in the clearest possible manner and provide contact addresses for visitors who seek further information or support. The Webmaster will display his or her e-mail address clearly throughout the Web site.
Transparency of Sponsorship	Support for this Web site will be clearly identified, including the identities of commercial and noncommercial organizations that have contributed funding, services, or material for the site.
Honesty in Advertising and Editorial Policy	If advertising is a source of funding, it will be clearly stated. A brief description of the advertising policy adopted by the Web site owners will be displayed on the site. Advertising and other promotional material will be presented to viewers in a manner and context that facilitates differentiation between it and the original material created by the institution operating the site.

HON = Health on the Net Foundation; HTML = hypertext markup language.
Reprinted with permission from Health on the Net Foundation. HON Code of Conduct (HONCode) for medical and health Web sites. *www.hon.ch/HonCode/Conduct.html*.

Table 1-11. Useful Web sites

Web Site	Web Address	Information Available on Web Site
Agency for Healthcare Research and Quality	*www.ahcpr.gov*	Online clinical practice guidelines for disease states
AIDS Treatment Information Service	*www.hivatis.org*	Living documents for treatment guidelines related to HIV/AIDS
American Academy of Pediatrics	*www.aap.org*	Information on pediatric issues, including news releases and guidelines
American College of Chest Physicians	*www.chesnet.org*	Practice guidelines and consensus statements
American Medical Association	*www.ama-assn.org*	Web site for the AMA. Links to JAMA online and Archives journals
American Pharmaceutical Association	*www.aphanet.org*	A variety of information related to pharmaceutical care, professional development, and governmental affairs
American Society of Clinical Oncology	*www.asco.org*	ASCO guidelines
American Society of Consultant Pharmacists	*www.ascp.com*	The Consultant Pharmacist journal and guidelines on long-term care
American Society of Health-System Pharmacists	*www.ashp.org*	Much useful information, including position statements, therapeutic guidelines, drug shortages, and pharmacy news
American Society of Parenteral and Enteral Nutritionists	*www.clinnutr.org*	Guidelines for use of parenteral and enteral nutrition
American Thoracic Society	*www.thoracic.org*	Consensus statements and position papers on respiratory medicine
Cardiosource	*www.cardiosource.com*	Cardiology-focused Web site, containing trial news, cardiology journals, and links to the American College of Cardiology/American Heart Association guidelines
Centers for Disease Control and Prevention	*www.cdc.gov*	The online version of Morbidity and Mortality Weekly Report, information on traveler's health, and CDC prevention guidelines
Centerwatch	*www.centerwatch.com*	Information on ongoing clinical trials
Clinical Trials	*www.clinicaltrials.gov*	Information on ongoing clinical trials
Doctor's Guide	*www.docguide.com*	Contains daily health news updates, new drugs/indications, and Web casts
Emedicine	*www.emedicine.com*	Free access to online textbooks
FDC Reports	*www.fdcreports.com*	Online version of the pink sheets and various other sheets
Food and Drug Administration	*www.fda.gov*	Medwatch, drug labeling, orphan drugs, and the electronic orange book
Infectious Diseases Society of America	*www.idsociety.org*	Various infectious diseases guidelines
Institute for Safe Medication Practices	*www.ismp.org*	Information on error reporting and drug safety
Joint Commission on Accreditation of Healthcare Organizations	*www.jcaho.org*	Information on JCAHO standards for various practice settings
MD Consult	*www.mdconsult.com*	Current version contains more than 30 major textbooks
Medical Letter	*www.medicalletter.com*	Online version of Medical Letter
Medscape	*www.medscape.com*	Contains medical news, review articles, free full text for selected journals, and personalized e-mail updates
Merck Manual	*www.merck.com*	Provides free access the Merck Manual
National Guideline Clearinghouse	*www.guideline.gov*	Lots of guidelines
National Institutes of Health	*www.nih.gov*	Links to many health-related institutes and centers
Natural Database	*www.naturaldatabase.com*	Online version of Natural Medicines Comprehensive Database
Oncolink	*www.oncolink.com*	Searchable Web site focused on cancer therapy
Pharmaceutical Research and Manufacturers of America	*www.phrma.org*	Information on the drug development and approval process
Pharmacist's Letter	*www.pharmacistsletter.com*	Online version of Pharmacist's Letter
RxAssist	*www.rxassist.org*	Information on pharmaceutical patient assistance programs
Torsades de pointes/drugs that prolong the QT interval	*www.torsades.org*	A list of drugs that prolong the Q-T interval and/or induce torsades de pointes
United States Pharmacopoeia	*www.usp.org*	Information on drug standards and dietary supplements

AIDS = acquired immune deficiency syndrome; AMA = American Medical Association; ASCO = American Society of Clinical Oncology; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; JAMA = Journal of the American Medical Association.

Annotated Bibliography

1. Malone PM, Mosdell KW, Kier KL, Stanovich JE, eds. Drug Information: A Guide for Pharmacists, 2nd ed. New York, NY: McGraw-Hill Companies, 2001.

   The goal of this reference is to educate the practicing pharmacist or the pharmacy student on how to effectively search, evaluate, and communicate drug information. The first chapter introduces the concept of drug information and areas in which drug information specialists are employed. The next several chapters review the systematic approach to answering questions, formulating drug information responses, drug information resources, and literature evaluation. The literature evaluation chapters provide a thorough review of how to evaluate a report of a clinical trial, including each section of an article. Different types of trial designs also are explained. The chapter about statistics reviews descriptive and inferential statistics as well as a variety of statistical tests. Additional chapters in the book that are not directly related to literature evaluation include pharmacoeconomics, drug misadventures, pharmacy and therapeutics committee, and the drug use process. The chapter about professional writing helps readers understand the publication process. The book also contains numerous appendices that contain many useful lists and examples, including drug information resources by topic, drug monograph format, questions to ask when evaluating the primary literature, and Web addresses. In addition, each chapter contains many examples and is extensively referenced.

2. Altman DC, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–94.

   The Consolidated Standards of Reporting Trials statement, initially published in 1996 and updated in 2000, was created to improve and standardize the reporting of clinical trials in the literature and to help facilitate literature evaluation. It was developed by an international group of clinical researchers, statisticians, epidemiologists, and biomedical editors, and is supported by a large number of medical and health care journals and editorial groups. The Consolidated Standards of Reporting Trials statement includes a list of items that should be addressed in all clinical trials and a flow diagram for documenting the patients at each stage of the trial. The document addresses each item in the checklist thoroughly with examples from the literature and an explanation of why addressing the item is important. A glossary of terms also is included.

3. Riegelman RK, Hirsch RP. Studying A Study and Testing A Test: How to Read the Medical Evidence, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000.

   This is the fourth edition of an excellent text about evaluating the literature. The book is divided in to five sections: studying a study, testing a test, rating a rate, considering costs and evaluating effectiveness, and selecting a statistical test. The first section provides a thorough review of the many aspects of clinical trial design that should be considered when evaluating the literature. The authors describe theoretical examples that help the reader apply the concepts to a clinical scenario. The other sections provide the reader with additional skills necessary for evaluating clinical trials, such as understanding diagnostic statistical tests, and applying rates.

4. Cuddy PG, Elenbaas RM, Elenbaas JK. Evaluating the medical literature. Part I: abstract, introduction, methods. Ann Emerg Med 1983;12:549–55.

5. Elenbaas RM, Elenbaas JK, Cuddy PG. Evaluating the medical literature. Part II: statistical analysis. Ann Emerg Med 1983;12:610–20.

6. Elenbaas JK, Cuddy PG, Elenbaas RM. Evaluating the medical literature, Part III: results and discussion. Ann Emerg Med 1983;12:679–86.

   Although these references are more than 20 years old, they provide an excellent review of each section of a clinical trial and are still used as standard references for many drug information courses and rotations. These articles are easy to read and include many examples of what to look for when evaluating a clinical trial. The article about methods explains trial design, inclusion and exclusion criteria, sampling, randomization, controls, blinding, and outcome measures. Common mistakes are identified and methods to avoid these mistakes are discussed. The statistics article is a concise review of the most common statistical methods focusing on interpretation. The article is in a question-and-answer format and highlights the most common flaws found in the medical literature.

7. Wilson P. How to find the good and avoid the bad or ugly: a short guide to tools for rating quality of health information on the internet. BMJ 2002;324:598–602.

   This article reviews the methods available for evaluating health-related Web sites and provides the reader with a basic understanding of these methods. Codes of conduct, quality labels, user guidance systems, filtering tools, and quality and accreditation labels are defined and costs and benefits of each are discussed. Specific references to organizations and their Web sites are included for each of the methods discussed. This article is appropriate for anyone who is unfamiliar with the various ways to rate the quality of Web sites.

8. Guyatt G, Rennie D, eds. The Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. Chicago, IL: American Medical Association, 2002.

   This book grew out of a series of 25 articles published in JAMA between 1993 and 2000, which are the original Users' Guides to the Medical Literature. Clinicians have found this book, which includes contributions by about 50 experts in evidence-based medicine, to be invaluable. The book is divided into two parts. The first part covers the basics of evaluating and applying the medical literature. This part identifies and elaborates on three questions to evaluating an article: Are the results of the study valid? What are the results? and How can I apply these results to patient care? The second part of the book, "Beyond the Basics: How to Assess and Teach" is for clinicians who want to understand evidence-based medicine on a much deeper level. This book is available in both paper and electronic (CD-ROM and Web-based) formats.

Please start new PSAP-V answer sheet before continuing.

SELF-ASSESSMENT QUESTIONS

1. A physician in your hospital wants to start all of his patients admitted to the intensive care unit on a proton-pump inhibitor. He states that a recent study in hospitalized patients found that proton-pump inhibitors improved survival when used for stress ulcer prophylaxis. You realize that this will increase the pharmacy's budget considerably and want to thoroughly evaluate the evidence. Which one of the following statements is true regarding your evaluation of this article to which the physician refers?
   A. The inclusion and exclusion criteria should be evaluated to determine if the patient population is similar to your patient population before using the study results to make a decision.
   B. If a significant difference was found between the two groups, then the possibility of a type II error must be considered.
   C. It is not necessary to review the competency of the authors by reviewing their affiliations and credentials.
   D. The methods used to blind the study are not important because the outcome was objective.

2. As a pharmacist in an anticoagulation clinic, you want to develop a reference library to guide you when evaluating the clinical significance of possible drug interactions. Which one of the following types of references is best suited for this purpose?
   A. Primary references.
   B. Secondary references.
   C. Tertiary references.
   D. Internet.

3. A community hospital has decided to switch all its patients to atorvastatin from simvastatin for cost reasons. The pharmacist decides to conduct a study examining the effects of this switch on patient cholesterol profiles and total cost. The pharmacist does not want to predict the direction of the study effect (i.e., positive or negative). Which one of the following is an appropriate objective for this study?
   A. The objective of this study is to examine the safety and efficacy of simvastatin compared to atorvastatin and the comparative cost of each therapy at a community hospital.
   B. The objective of this study is to examine the results of switching from simvastatin to atorvastatin on lipid profiles and cost-savings associated with the switch at a community hospital.
   C. The objective of this study is to examine the safety and efficacy of simvastatin compared to atorvastatin and the cost-savings associated with the switch at a community hospital.
   D. The objective of this study is to examine the results of switching from simvastatin to atorvastatin on lipid profiles and the comparative cost of each therapy at a community hospital.

4. As an oncology pharmacist at a large tertiary care center, you determine that one of your patients is experiencing Stevens-Johnson syndrome. The patient recently was started on Curemesis, an antiemetic you frequently recommend for your patients. After reviewing pertinent tertiary references, you learn that Curemesis has been associated with Stevens-Johnson syndrome in less than 1% of patients. When researching this further trying to determine symptoms of the reaction and what other clinicians have done to manage patients experiencing Stevens-Johnson syndrome caused by Curemesis. Which one of the following types of clinical trial design is the best source to find the information you need?
   A. Randomized, controlled trial.
   B. Case report or case series.

C. Meta-analysis.
D. Case-control study.

5. A new drug is indicated for type 2 diabetes mellitus by the Food and Drug Administration (FDA) based on a single randomized, controlled trial. The patients you see in the clinic primarily are men and women older than 50 years of age with concomitant cardiovascular disease. You also have many patients who have failed to benefit from therapy with sulfonylureas and metformin. Which one of the following will most likely affect your ability to extrapolate the results of this trial to the patients in your clinic?
   A. The inclusion criteria of this study were men and women older than 18 years of age with type 2 diabetes mellitus.
   B. The exclusion criteria were a history of cardiovascular disease, liver disease, and concomitant use of insulin.
   C. The mean age of the patient population studied was 52.5 years of age and 60% of the population was male.
   D. A majority of patients' disease included in the study had been uncontrolled on metformin.

6. As a drug information specialist working in the call center at a university hospital, you receive a call from a physician who wants to prescribe a cyclooxygenase-2 inhibitor to a patient with aspirin-induced asthma. He wants to know if there are any specific precautions or contraindications with cyclooxygenase-2 use in this population. Which one of the following approaches is best to take when answering this question?
   A. An Internet search followed by a call to the pharmaceutical company and a MEDLINE search.
   B. A MEDLINE search and a review of the clinical trials assessing the question.
   C. A review of the tertiary literature for contraindications and precautions followed by a MEDLINE search and a review of the primary literature.
   D. A review of the primary literature followed by a call to the pharmaceutical company.

7. You are a drug information pharmacist and receive a call from a consumer requesting general information on a new drug for Alzheimer's disease that was just approved for marketing by the FDA yesterday. The caller claims he heard a news report on this new drug but all he can remember is the name of the pharmaceutical company that manufactures the drug. Which one of the following references is best to check initially?
   A. Physician's Drug Reference.
   B. MEDLINE.
   C. Internet.
   D. International Pharmaceutical Abstracts.

8. You are a member of the pharmacy and therapeutics committee at your hospital. The hospital is considering adding levalbuterol to the formulary. Most of the comparative studies with levalbuterol demonstrate that it is similar in efficacy to albuterol with a small difference in favor of levalbuterol in the effect on heart rate. One comparative study found levalbuterol to be associated with a shorter length of hospital stay and decreased hospital costs. However, this study was a retrospective chart review. Which one of the following is true regarding this literature?
   A. The retrospective design of this study makes the results subject to recall bias.
   B. Levalbuterol should be added to the formulary based on the potential cost-savings as demonstrated in the retrospective study.
   C. Retrospective studies are the strongest means by which to determine cause and effect.
   D. Levalbuterol should be added to the formulary based on its improved safety of heart rate shown in comparative trials.

9. Parknia is a new drug with Parkinson's disease as its labeled use. The drug's labeling is based on the results of three randomized, placebo-controlled trials. The doctors in your clinic want to start prescribing the drug, but they want to know how it compares to the drugs they currently use. You conduct a MEDLINE search to see if any newer trials have been published on the drug and find two randomized, controlled trials that compare Parknia to drugs in current use. Both studies concluded that Parknia was similar in efficacy to the other drugs. Which one of the following is true regarding the evaluation of these studies?
   A. The doses of the comparative drugs should be the same as those used in clinical practice.
   B. The possibility of type I error should be considered.
   C. Because the two studies are not placebo-controlled the results are invalid.
   D. If the study sponsor was disclosed, its role would not be important to evaluate.

10. Your pharmacy is considering purchasing a new secondary reference for searching adverse drug reaction reports. Your hospital is a large tertiary care center with a busy emergency department. Two references are being considered, ClinAlert and Reactions Weekly. Both of these references are abstracting services but there are other differences between these two references that could impact your purchasing decision. Which one of the following is the most significant difference between these two references that will affect your decision?
   A. ClinAlert is published more frequently than Reactions Weekly.
   B. ClinAlert contains brief summaries of the individual case reports.
   C. Reactions Weekly contains information on toxicology.
   D. Reactions Weekly covers about 100 journals.

11. You have been asked to find clinical studies on the efficacy of a new epilepsy drug, Epilstat, available only in Europe. A physician in your hospital attended a conference and wants information on the safety and efficacy of this drug. The problem is that most of the studies on Epilstat are in foreign journals. Which one of the following sources is the best to search for these foreign articles?
    A. Iowa Drug Information Service.
    B. MEDLINE.
    C. EMBASE.
    D. Journal Watch.

12. One of your colleagues has noticed that more pharmacy technicians have latex allergy. You wish to determine the prevalence of latex allergy in a population of pharmacy technicians. Which one of the following clinical trial designs is best suited for this purpose?
    A. Randomized, controlled, clinical trial.
    B. Case-control study.
    C. Cohort study.
    D. Cross-sectional study.

13. A new drug, Superstatin, is indicated for treating hyperlipidemia; however, the FDA is concerned that this drug may cause liver toxicity. There were a couple reports of liver toxicity before the drug came to the market; however, not enough to conclude an increased risk for liver toxicity. Which one of the following study designs is best suited to identify if an increased risk for liver toxicity exists with Superstatin?
    A. Randomized, controlled, clinical trial.
    B. Case-control study.
    C. Prospective cohort study.
    D. Cross-sectional study.

14. There have been a few reports that low-dose aspirin may decrease the risk for certain types of cancer. You have a large population of patients with colon cancer at your hospital and you want to conduct a study to determine if the use of low-dose aspirin is associated with a reduced risk of developing colon cancer. Which one of the following clinical trial designs is best suited for this purpose?
    A. Randomized, controlled, clinical trial.
    B. Case-control study.
    C. Prospective cohort study.
    D. Cross-sectional study.

15. You are appraising a meta-analysis of studies measuring the association between pediatric vaccinations and the development of autism. You are trying to determine if you need to warn the parents of your pediatric patients of the risk. Which one of the following is true regarding the evaluation and application of the results of this meta-analysis?
    A. If the investigators searched MEDLINE and the reference lists of all identified articles, the study would be at increased risk for publication bias.
    B. The conclusions of this meta-analysis are stronger than those in a randomized, controlled trial and should be used to guide clinical practice.
    C. One disadvantage of meta-analyses is that they increase the chance for type II error.
    D. One advantage of meta-analyses is that they increase the heterogeneity of the studies being analyzed which improves the statistical analysis of the results.

16. You are a clinical pharmacist on the transplantation team. A nurse on the floor asks for a chart that lists the most common side effects of the drugs commonly used in patients receiving transplants. You will need to complete this chart as quickly and efficiently as possible. Which one of the following references is the best initial source of information to answer this question?
    A. The Internet, as long as the Web site displays the Health on the Net Foundation logo.
    B. Facts and Comparisons because its charts will summarize the information.
    C. A review article on immunosuppression after organ transplantation.
    D. The Physician's Drug Reference because it will be the most complete.

17. Which one of the following titles best describes a study for treating type 2 diabetes with either pioglitazone or rosiglitazone without bias?
    A. Pioglitazone is superior to rosiglitazone for treating type 2 diabetes.
    B. A comparison of pioglitazone and rosiglitazone for treating type 2 diabetes.
    C. The efficacy and safety of pioglitazone and rosiglitazone for treating diabetes.
    D. The use of two thiazolidinediones for treating type 2 diabetes.

18. You are evaluating a cohort study on the relationship between alcohol consumption and the development of certain types of cancer. The investigators included 300 patients who drank more than 12 ounces/day of alcohol and 300 patients who do not drink alcohol. The risk for developing cancer was 20-fold higher in the patients who drank alcohol compared to those who did not. The authors also found that cigarette smoking was more common in the alcohol drinking group. Which one of the following limitations or biases is most likely to have occurred in this study?
    A. Confounding.
    B. Decreased external validity.
    C. Increased internal validity.
    D. Prevalence bias.

19. You are analyzing the results of a case-control study of the effects of ephedra use on weight loss. Patients who had lost weight during the past 6 months were identified. The cases were the patients who had used ephedra to lose weight, whereas the controls were

patients who had not used ephedra to lose weight. The cases were questioned regarding the amount of ephedra they had taken, others methods used to lose weight, and the total amount of weight lost while taking ephedra. The control group also was questioned about methods used to lose weight and how much their weight had fluctuated during the same time period. Which one of the following is your biggest concern with the methods of this study?

A. External validity.
B. Blinding.
C. Randomization.
D. Recall bias.

20. You are a drug information specialist and you receive a question about the effect of long-term use of propofol on kidney function. Which one of the following search strategies would be the best way to find this answer? (The search references in the answer choices are listed in the order in which you would check them.)

A. Internet, MEDLINE, and Facts and Comparison.
B. MEDLINE, International Pharmaceutical Abstracts, and EMBASE.
C. The United States Pharmacopeia Dispensing Information, International Pharmaceutical Abstracts, and Current Contents.
D. American Hospital Formulary Service, MICROMEDEX, and MEDLINE.